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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

65TH MEETING

Thursday, March 16, 2000

8:30 a.m.

Holiday Inn Bethesda
Versailles I and II
8120 Wisconsin Avenue
Bethesda, Maryland

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

PARTICIPANTS

Richard L. Schilsky, M.D., Chairman
Karen M. Templeton-Somers, Ph.D., Executive Secretary

MEMBERS

Kathy S. Albain, M.D.
David H. Johnson, M.D.
David P. Kelsen, M.D. (Eloxatine only)
Scott M. Lippman, M.D.
Kim A. Margolin, M.D.
Stacy R. Nerenstone, M.D.
Victor M. Santana, M.D.
Richard M. Simon, D.Sc.
George W. Sledge, Jr., M.D.

Jody L. Pelusi, F.N.P., Ph.D., Consumer Representative
Sallie Forman, Patient Representative

FDA

Rachel Berman, M.D.
Isagani Chico, M.D. (Camptosar only)
Steven Hirschfeld, M.D. (Eloxatine only)
John Johnson, M.D. (Eloxatine only)
Robert Justice, M.D.
Grant Williams, M.D. (Camptosar only)

C O N T E N T S

C O N T E N T S

P R O C E E D I N G S

Call to Order and Opening Remarks

DR. SCHILSKY: Good morning. Welcome to the 65th Meeting of the Oncologic Drugs Advisory Committee. I would like to begin by introducing the committee members. Why don't we begin with Dr. Santana.

Introduction of Committee

DR. SANTANA: Victor Santana, pediatric oncologist, St. Jude Children's Research Hospital.

DR. ALBAIN: Kathy Albain, medical oncologist, Loyola University, Chicago.

DR. LIPPMAN: Scott Lippman, medical oncologist, M.D. Anderson Cancer Center.

DR. MARGOLIN: Kim Margolin, medical oncology and hematology, City of Hope, Los Angeles.

DR. SLEDGE: George Sledge, medical oncologist, Indiana University.

DR. D. JOHNSON: David Johnson, medical oncologist, Vanderbilt University.

DR. PELUSI: Jody Pelusi, oncology nurse practitioner in Arizona. I sit as the consumer representative.

DR. NERENSTONE: Stacy Nerenstone, medical oncology, Hartford, Connecticut.

DR. SCHILSKY: Richard Schilsky, medical

oncologist, University of Chicago.

DR. TEMPLETON-SOMERS: Karen Somers, Executive Secretary to the Committee, FDA.

DR. KELSEN: Dave Kelsen, medical oncologist, Memorial Sloan Kettering.

MS. FORMAN: Sallie Forman, patient representative.

DR. HIRSCHFELD: Steven Hirschfeld, medical officer, FDA.

DR. J. JOHNSON: John Johnson, clinical team leader, FDA.

DR. BERMAN: Rachel Berman, Deputy Director, Office of Drug Evaluation I.

DR. SCHILSKY: Thank you.

Dr. Somers will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. TEMPLETON-SOMERS: Good morning.

The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the participants, it has been determined that all interest in firms regulated by the

Center for Drug Evaluation and Research which have been reported by the participants present no potential for a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. 208, full waivers have been granted to Dr. Richard Schilsky, Dr. David Kelsen, Dr. Scott Lippman, Dr. Kim Margolin, Dr. Victor Santana, and Dr. George Sledge.

A copy of these waiver statements may be obtained by submitting a written request to the FDA's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

In addition, we would like to note that Dr. Douglas Blayney is excluded from participating in all matters concerning Eloxatine.

Further, we would like to disclose that Dr. Kathy Albain and Dr. Richard Schilsky have involvements which do not constitute a financial interest in the particular matter within the meaning of 18 U.S.C. 208, but which may create the appearance of a conflict.

The Agency has determined notwithstanding these interests that the interests of the Government and the participation of Drs. Albain and Schilsky outweighs the appearance of a conflict. Therefore, they may participate fully in all matters concerning Eloxatine.

In the event that the discussions involve any

other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous involvement with any firm whose products they may wish to comment upon.

Thank you.

I would also like to apologize for the crowded conditions. This was the only space that we could get. I think it is more important that we hold the meeting. There is a monitor in the lobby where, if you are tired of standing and want to walk around, you can go out and watch the slides from there and hear the presentation.

In addition, we would like to invite those of you who cannot find a seat in the back, may sit in the back part of the FDA section.

Thank you.

DR. SCHILSKY: Thank you.

Open Public Hearing

We have a few minutes for an open public hearing. I understand that there are three individuals who have requested time to address the committee.

Is Kathleen Murray here? Please come to the podium, identify yourself, and tell us if you have received any support to attend the meeting today.

MS. MURRAY: I am Kathleen Murray from Summit, New Jersey, and I didn't receive a dime to come here unfortunately, although I did kind of ask about that.

I was asked to attend this by my oncologist at Thomas Jefferson University. I did ask her, you know, well, exactly what is this, because I didn't realize that they had advisory committees for different drug groups, because I know cardiac doesn't, so I was kind of surprised at this.

Then, I asked her what would you like me to say, and I didn't get any answers to that either, and I asked my other oncologist in northern New Jersey, because I live in New Jersey, I travel two hours to Philadelphia for oxaliplatin, and I got a little bit more help from him, so I am going to start into this. If you have any questions, interrupt me or I will answer them at the end, but I have a specific reason for being here.

My history is I had rectal carcinoma in '97. I had an initial minor surgery. I had a T1 level, you know, problem, and then I had recurrence a year later. I went to Sloan Kettering with Alfred Cohen, who did surgery, and it was eight hours, and there wasn't much left after he finished with me.

I did not do prophylactic chemotherapy after that point. With the initial surgery, I did chemotherapy and radiation, and we did interoperative radiation at Sloan Kettering, and that is the reason I went there.

In March of '99, my CEA started to climb again, so I started into the next phase, which was CPT-11. By September it was apparent that this was not particularly a protractive drug for me, and at that point I was back at Sloan Kettering with Kemeny, and she recommended oxaliplatin, and I was qualified for it, and she said that there is a wait list. So, I was put on the wait list.

I will get into the wait list problem later because I know many of you know about it, but I was very concerned about that.

As far as my experience with oxaliplatin, I am only into the second, six-week cycle of this, but I have been through 5-FU/leucovorin, I went through CPT-11, and I think this is a relatively easy drug to take. I mean I don't really have any problems with it.

The neurotoxicity, I don't really consider it toxicity, I consider it a side effect, you know, and as long as you follow the rules, you don't have the effect, the sensation of neurotoxicity that feels like you have stuck your finger in an electrical outlet.

There are a few other side effects. I did have

two of them, but they were my fault, and you just learn not to do that again.

As far as the nausea and vomiting, I don't have anything like that at all. At Thomas Jefferson, I kind of asked general questions of how their population is doing, and I know Edith Mitchell has well over 100 patients in her study, so I mean that is a good population to talk about, and she wouldn't give me that information either. She said, you know, you have to go to this.

So, the next group you go to are nurses, who, you know, talk to patients constantly, and they said they didn't think the nausea and vomiting problem was that great, most of the people generally have just anorexia, and they didn't think it was that serious.

As far as the diarrhea goes, you will get that, because you are usually on oxaliplatin and one other drug, and I am on 5-FU/leucovorin along with this. So, the combination of the two produces a problem, but it is manageable by drugs, and you are tired, but, you know, that goes along with chemotherapy, and you can have low counts, but that is manageable, and you just watch the neurological effect, which I thought was kind of entertaining in the beginning, to see, you know, exactly how you felt with it.

What I am here for is that I am asking for an expedited review of this drug. It has been in Europe for

quite a number of years without very many problems apparently, and the problem in this country is that there are I think 180 sites around the country.

The problem I had was when I talked to Kemeny in October, the wait list she had was estimated to be two months. So, I called in early December to find out about what time I would start, and I was told at that time that there 30 to 40 people ahead of me on the list. Even with attrition on a regular list, it just looked like it was going to be way down the line.

At that point, from October to December, those tumors are growing extensively. So, I then said what their estimated time was, and they said somewhere around late February, March, so that is now five to six months down the line.

I said, well, okay, who else is offering this drug, and there were only three sites in Manhattan, one outside of Manhattan, so I got all the names of the places from Yale to Philadelphia. I called all the sites, and I got on the wait list at five or six sites currently.

Sloan Kettering did call in late January and said that they had a place for early February, and so from early December to now, I haven't heard from one other site.

Now, the third problem you have is Katie Couric did her presentation last week for five days. The last

date, the oncologist from Dana Farber listed three drugs for the treatment of colorectal, two of which we know aren't that great, I mean the 5-FU has been probably around longer than some of the people in this room. CPT-11 is a little bit better, some people respond to it.

This drug has doubled, almost tripled the response rate, and he announced that there were three drugs - 5-FU/ leucovorin, CPT-11, and oxaliplatin.

I am concerned, what is the American public going to do when they find out that they can't get on this drug, and that this drug is--I have listened to since last spring, from Cohen at Sloan Kettering it should be out soon, and it's still not out.

So, I am asking this committee for an expedited review or this committee to recommend an expedited review to FDA based on the European studies and limited problems with this drug currently.

That's it. Any questions?

DR. SCHILSKY: Thank you very much.

MS. MURRAY: Okay.

DR. SCHILSKY: The next speaker is Mary McCarthy. Is Mary McCarthy here?

[No response.]

DR. SCHILSKY: Okay. Richard Farrell? Please come to the podium and identify yourself, and tell us

whether you have received any support to be here today.

MR. FARRELL: Good morning. I expected a small crowd. This is intimidating, but we will get through it.

My name is Richard Farrell. I am speaking on behalf of the Colon Cancer Alliance, and I am a member of the Colon Cancer Alliance's board of directors.

The Colon Cancer Alliance is a patient-focused volunteer nonprofit organization dedicated to education, patient support, and research. We advocate for increased attention to, and funding for, colorectal cancer awareness, prevention, and research efforts.

We are colorectal cancer survivors, their caregivers, and their family and friends.

For the record and in the interest of clear disclosure, the Colon Cancer Alliance is working with Sanofi Lily Oncology Company, Pharmacia & Upjohn, and other corporations to provide information and support to people touched by colorectal cancer and to increase their awareness of this disease.

At the same time, we want to make clear that this statement reflects only the Colon Cancer Alliance's perspective, work, and review. In addition, we are attending this meeting at our own expense.

We are not here to give highly technical comments on the application before you today. We understand that

your decisions were based on the scientific evidence of the efficacy and safety, as they should be.

We ask that as you consider the evidence, remember that there are people like me whose lives depend on the availability of effective treatment options for colorectal cancer. Treatment options for colorectal cancer are very limited.

Until recently, there was just one option - 5-FU. Now, there are two and patients who fail or no longer respond to 5-FU can proceed to Camptosar. About 15 to 20 percent of late stage patients respond to each of these drugs. On average, the late stage patients treated with 5-FU survive six or seven months while those treated with Camptosar survive nine to 10 months. Clearly, these two treatment options are not enough. If colorectal cancer patients are to survive longer and live better, additional treatment options are critical.

Treatment options provide a chance for longer survival and, as importantly, they provide hope, hope that if one treatment isn't effective, there is another weapon in the arsenal, hope, that while a treatment may not cure our disease, it may provide us with more time.

Frequently, our members ask I have failed 5-FU and CPT-11, now, what do I do? Given the number of colorectal cancer treatment options currently in late stages of

development, we look forward to the day when we can provide a satisfactory answer to that question.

We urge you to keep this pressing need for options in mind as you consider the evidence before you. I am part of that evidence, a Stage III colorectal cancer survivor who stands here today because of options in treatment available only through clinical trials at this time.

On behalf of the many members of the Colon Cancer Alliance, we thank you for hearing our comments today, but, now, on a personal note, very briefly, a year ago this past January I was operated on in my hometown, I was cut open, and I was sewed up, and I was told to go home and settle my affairs because I had no chance for survival.

I did not accept that death sentence. I contacted Memorial Sloan Kettering and Dr. Nancy Kemeny, and I was put into a trial of oxaliplatin and CPT-11 in the fourth cohort. In the eight months I was in that program, my tumors reduced far enough, so that I was able to have additional surgery and they removed five tumors from my lower intestinal area.

As of last week, with my latest CT scan, I am now tumor free, and I hope to remain that way, but in the meantime, the only reason I am here today speaking to you is because I was able to have access to oxaliplatin and CPT-11, and I hope that you will take proper action to provide this medication to all the tens of thousands of people who so

eagerly need it, and I thank you very much.

DR. SCHILSKY: Thank you very much.

Is there anyone else in the audience who would like to address the committee?

[No response.]

DR. SCHILSKY: If not, then, we will continue with the agenda.

Before we get to the discussions about Eloxatine, we will have a presentation by Dr. Pazdur on Pediatric Exclusivity Drug Development Plan.

Pediatric Exclusivity Drug Development Plan

DR. PAZDUR: Thank you, Richard.

I wanted to bring this forward to the ODAC Committee. We over the past several months in the division have been working on a drug development plan for pediatric oncology drugs, and I wanted to really go over this, so you have some understanding what we have been doing in the division, our discussions with the various pediatric groups, industry sponsors, and the pediatric patient community and advocacy community.

[Slide.]

Before doing that, I want to go over the current regulations regarding pediatric drug development. Like most things in government, they are easy, but somehow we make them very complicated, and a lot of this has to do with the

nomenclature surrounding the pediatric regulations.

There are two major regulations that I would like to talk about, one being the FDAMA or the Food and Drug Modernization Act of 1997, and the second one being the 1998 Pediatric Rule.

One of our reviewers, Steve Hirschfeld, who has been working on this project for a long time, refers to these two as the carrot and the stick regarding pediatric drug development, and I think that you will see as I explain these two regulations why he uses that nomenclature.

Well, the Food and Drug Modernization Act of 1997 is what we call the carrot, and basically, this is a voluntary program for a six-month extension to existing marketing exclusivity or patent protection for the entire product line if an active moiety is capable of providing new pediatric information that will benefit the public health.

The submissions must come in response to an FDA written request, however, proposals can be submitted to the agency for a written request from a variety of sources. They can come from sponsors, they can come from cooperative groups, they can come from the academic community or investigators.

[Slide.]

In contrast, the Pediatric Rule of 1998 is a mandate, and this is what we refer to as the "stick,"

because it is a mandate. What this rule stipulates is that a product under review must--remember the word "must"--provide pediatric information if the indication under review is a disease found in children.

If the disease is not found in children, a waiver may be granted or a partial waiver. So, there are important differences here. The FDAMA regulation basically is a regulation that is voluntary, that is an attempt to expand the use of pediatric drugs. Likewise, the Pediatric Rule is a rule aimed at expanding the use of drugs in pediatrics.

The problem with medical oncology and pediatric oncology is that sometimes the indications that we find in adult diseases, especially adult malignancies, don't translate well into the pediatric disease community, the pediatric oncology community, making the implementation of the Pediatric Rule of 1998 somewhat difficult in pediatric oncology.

[Slide.]

Listed here is a comparison of the Rule, the FDAMA regulation on the first side, and the Rule on the other side. As I stated before, the FDAMA regulation is voluntary, the 1998 Rule is mandatory.

FDAMA applies to the entire product line. There is no restriction on eligible pediatric diseases. It only applies when there is an underlying patent or exclusivity

protection. Biologicals are excluded and orphan products are included.

In contrast, as I stated before, the 1990 Rule attempts to extrapolate diseases that are found in both children and adults. If the drug is under development in the adult indication, it is required that the pediatric studies be performed.

Again, this is somewhat difficult in medical oncology and pediatric oncology, because the diseases are not as well linked as in other therapeutic disciplines. In addition to this, the 1990 Rule applies to biologicals and orphan drugs are excluded.

[Slide.]

I would just like to show you and spend time on the Pediatric Exclusivity, the FDAMA regulation, because this is where the pediatric development plan really takes its muscle and the incentive for industry to become and have a greater involvement in pediatric drugs.

As I stated before, proposed pediatric study requests can come from a variety of sources - industry, industrial sponsors, cooperative groups, academics, private practitioners. They come to the FDA, a written request is generated from the FDA.

This written request is highly specific or greatly specific. It gives the details, the numbers of patients

that must be enrolled in a trial. This subsequently leads to the submission and the study reports after the studies are completed, and then the FDA makes a determination whether the exclusivity should be extended to the drug.

I would like to emphasize--and this is a key aspect of the FDAMA regulation--that the extension of exclusivity is not based solely on the results of the trial, but based on meeting the stipulations provided in the written request.

In other words, a sponsor can get a patent protection or exclusivity, an extension of exclusivity by meeting the requirements of the written request irrespective of the results of a trial. Hence, if a trial is negative, does not show any therapeutic results, the sponsor can still get exclusivity based on this existing FDAMA regulation.

[Slide.]

What has been the FDA experience with the FDAMA incentive? When one takes a look at pediatrics overall, it has been very, very successful. Proposals received since its inception has been about 163 proposals, with written requests issued, about 127.

In oncology, we have a different picture. We have only received five proposals, and only one written request has been generated. I think that this points to some unique differences in pediatric oncology versus other pediatric

disciplines.

I think the predominant one is that we are dealing with a relatively small number of patients that have pediatric malignancies, and there has been really some confusion on what we are looking for in the pediatric implementation, pediatric oncology implementation of FDAMA.

The proposals that we received for oncology basically were only these five proposals, were only proposals looking at dose-seeking studies and toxicity studies, and clearly, the intent as we perceived it of this regulation was really to establish and move the field forward in discovering new pediatric drugs.

Therefore, we have stipulated in our development plan that there needs to be an efficacy or an activity component, not simply a Phase I study to be performed.

[Slide.]

Therefore, what we decided to do is basically, take the provisions of FDAMA, this incentive program, with the concept that one can get a patent extension even for meeting the regulations of the written request, but even in the light of having a negative efficacy study, and what we were looking for in developing the Pediatric Development Plan of oncology products is basically a good-faith effort from industry to develop drugs in pediatrics, and this is underscored, I think, when you examine our plan.

Basically, the overview of the plan requires dosing and pharmacokinetic studies in classical Phase I studies that pediatricians are I think well aware of doing in the pediatric oncology community.

It would, secondly, require Phase II or pilot studies in a potential range of indications if one was not obvious from preclinical or mechanisms of actions of the drug.

We would like to emphasize that this is not a supplemental NDA, since efficacy, the proof of efficacy, a clinical benefit is not required to be demonstrated in order to get the exclusivity extension.

The other point that we would like to point out about this plan is that this plan applies both to new molecular entities and drugs that have been already approved that have not been adequately investigated in pediatric oncology.

[Slide.]

The first stage of the program is listed here, and this is what I would assume to be a fairly classical Phase I development with some caveats regarding the FDAMA regulations.

The Phase I studies will determine the dose, pharmacokinetics, and toxicities, and we would plan roughly for about 25 patients. Here again, this would be negotiable

regarding what the drug was.

What is unique here in this plan is if unacceptable toxicity occurs, the development would be halted and exclusivity would be granted even if one has what one would consider possibly a negative Phase I study, in other words, excessive toxicity or prohibitive toxicity that would not allow further development of this drug.

Why are we doing this? We are interested in promoting and risk-sharing with the industry and encouraging pediatric drug development. We believe that this would be a very unique situation and a very unusual situation where there would be prohibitive toxicity which would prevent the drug from being further developed.

In the vast majority of cases, we would believe that the toxicity would be acceptable and we would proceed to the second stage of development of an agent.

[Slide.]

The second stage is basically the demonstration of clinical efficacy or I probably should use the word "activity" of the agent, and this would be Phase II studies, either single agent, add-on comparative designs, and/or pilot studies of combinations to demonstrate an agent's characteristics and contributions to efficacy, probably using surrogate endpoints and also provide, if positive, justification for further development to examine clinical

benefit.

[Slide.]

The possible outcomes of the Phase II studies are listed here. If efficacy is demonstrated, for example, by response rates, then approval would exist or could be granted under subpart H or full approval depending on the situation.

If there was no beneficial effect observed, development would be halted, and the extension of exclusivity still would be granted to the company on the entire product line.

If the results are promising, but not sufficient to support approval, a commitment to further development would be undertaken.

In all three cases, the granting of exclusivity would occur in the case of a subpart H approval, in the case of a study that failed to demonstrate efficacy, or in a situation where we saw some efficacy, but still will require further clarification of that efficacy.

Obviously, for the subpart H designation, that would still require a Phase IV commitment.

[Slide.]

The results of the completion of the Pediatric Development Plan are listed on this slide. The results of the plan would be summarized in a study report and submitted

to the FDA.

We are looking for good quality data, and we will be looking at the quality of this data and the conduct of the study. Even though we are granting exclusivity on the basis of what some people would term negative Phase II data, or a Phase I study that has demonstrated prohibitive toxicity, we would still like these studies to be conducted in an ethical, logical, and well done fashion.

Upon review, if the conditions of the initial written request are met, irrespective of outcome, a six-month exclusivity extension may be granted. In some cases, according to the FDAMA regulations, a 12-month extension can be granted if two indications are pursued in pediatrics.

We are looking for well-designed, well-executed studies, and a negative result can qualify, as I stated before, for pediatric exclusivity.

The intent of this plan is to use FDAMA in a good-faith effort for risk sharing as a prospective plan to develop and produce new information that is important to pediatric oncology.

We would like our sponsors to work quite closely with the existing pediatric community, the existing pediatric groups. This is not an effort to splinter pediatric drug development.

There have been tremendous accomplishments in

pediatric oncology regarding cures in this disease and demonstration of active agents, and we would like this to augment the success of pediatric oncology.

What we would like, though, is new molecular entities to be introduced early into the developmental plans of companies with regard to pediatrics.

In addition to this, I would like to emphasize that although we cannot mandate where studies occur with sponsors, we simply do encourage that they do open a dialogue with the pediatric oncology groups, with academic pediatric centers, really to further pediatric drug development.

This is a very important aspect for the division since I arrived, and I am committing resources to this. The first resources that we are committing is hiring additional pediatric oncologists in the division, really to augment the effort. We are in the process of also writing a guidance for both industry and participants in clinical trials regarding these regulations and this Pediatric Development Plan.

In addition to this, we will be having a subcommittee of ODAC, which will be labeled the Pediatric Oncology Subcommittee, and this will meet in September to examine the whole issue of pediatric drug development, FDA's involvement, and also potentially to look at some of these

FDAMA proposals that we get, and our written requests also.

Again, we look at this as a positive aspect to encourage pediatric drug development.

In ending, I would like to personally thank several people who have been very much involved with the development of this plan. We would greatly like to acknowledge the work of the pediatric advocacy community in really highlighting the need to pay special attention and refocus our interest in pediatric drug development.

I would like to give personal thanks to Dr. Steve Hirschfeld from our division who really has been the spearhead of pediatric development in the division, and also Patty Delaney and Joanne Miner from the Office of the Commissioner who has worked behind the scenes really to get the whole pediatric initiative moving in our division.

Thank you very much. I would be happy to answer any questions regarding this from the committee.

DR. SCHILSKY: Thank you, Rick.

Are there questions from the committee for Dr. Pazdur? Dr. Santana.

DR. SANTANA: I want to personally thank you for taking your time and presenting this to the group in a public hearing because I think, as I have commented with Dr. Hirschfeld on a couple of occasions, I think one of the difficulties has been in the community, not confusion, but a

lack of understanding of these two rules and how potentially they could be applied.

So, I congratulate the agency because I think we need to make a major educational effort at all levels, at the level of the sponsors, at the level of the community, at the level of this committee, at the level of the cooperative groups, to get a little bit better understanding of how these rules could be applied. So, I think educational efforts are going to consume some of our time in the next year or so.

So, I want to publicly thank you and the FDA for presenting this to us.

I have one point of clarification and then one question, and I will do the question first.

How is the agency going to measure success with these initiatives, within what time frame, within what variables? That is the question.

The point of clarification is if I understand the Pediatric Rule correctly, the three products that will we will be discussing today and tomorrow potentially fall under that under the new Pediatric Rule. Can you clarify that for me, too?

DR. PAZDUR: The measure of success would probably be in the subsequent approval of pediatric drugs, of pediatric oncology drugs, but I think from a surrogate

endpoint, we would probably be looking at the generation of written requests and the participation and acceptance of the pharmaceutical sponsors for accepting these written requests and developing the drugs.

As far as the three drugs that are under investigation regarding the Pediatric Rule, you know, the disease has to extrapolate to the pediatric community, and colon cancer, I would assume is not a pediatric disease unless you would like to clarify that.

DR. SANTANA: It is. It is not very frequent, there is very limited experience, but there are a number of pediatric patients who get this disease, and actually biologically and clinically, it is almost very similar to the adult disease. The AML is the same scenario.

DR. PAZDUR: As far as our proposals, we are in the process--rather than getting into any specific applications at this time--we are internally looking at agents that we are going to be generating written proposals on--written requests rather.

DR. SCHILSKY: Dr. Johnson.

DR. D. JOHNSON: I have some questions and some clarification for myself. How often can one receive an extension? For example, if a drug has a potential indication in children for a cardiac indication, but that same drug might also have an indication in oncologic areas,

can one get two, six-month extensions?

DR. PAZDUR: Yes, and it is for the entire product line, but it's a maximum of two according to the FDAMA regulations, and that could be added on orphan drug status, et cetera.

DR. D. JOHNSON: I have no idea if six months is a sufficient incentive.

DR. PAZDUR: But remember what is different here, Dr. Johnson, this is the entire product line, not for a specific indication, which makes it a real carrot. The fact that it has worked in other diseases in pediatrics, there are over 100 written requests generated on this, I think it does indicate in other diseases it has been effective.

DR. D. JOHNSON: When you say the entire product line, so every product that company X makes gets extensions?

DR. PAZDUR: No, for that drug.

DR. BERMAN: Can I clarify? It attaches to the active moiety, the six months, that is attached to the active moiety. We probably should ask the companies that are present what that means to them, but it apparently means a lot. We have been flooded with interest and requests, so this is clearly a tremendous incentive. We have never in our history seen such interest in supplements before this.

DR. PAZDUR: So, if the drug had an indication for an oncological in breast and colon and in leukemia, it would

be for all of those indications.

DR. D. JOHNSON: And then actually Dr. Santana touched on this, and I was going to ask what your definition of a pediatric disease, because clearly you, a colon expert, just said you didn't think colon cancer was a pediatric disease.

DR. PAZDUR: Let me answer that, and I think there is some confusion, and that is one of the reasons why we are going to have the subcommittee of pediatricians, because there isn't agreement on this, and I think what we will probably be looking at is incidence and we are going to establish a list of diseases where we think that this can extrapolate adults and children have the same disease.

You know, just because it happens once or is a rare disease, I don't know if that is the intent of the regulation.

DR. D. JOHNSON: It could take to the year 3000 to do the study. The final question I would have, and I am sure your subcommittee will work on this--and I applaud this, I actually think this is fantastic--but I am a little concerned about the concept of a negative Phase I trial leading to an extension or an approval of a product line. That bothers me.

DR. PAZDUR: We are going to be looking at that very, very carefully, obviously. We wanted to have this as

a provision to demonstrate a good-faith effort here, but we are not going to just blanketly look at a trial and if the trial had what we would term an equivocal toxicity grant exclusivity. That is for what I would interpret real toxicity that really prohibits further development of that drug.

We put that in with a great deal of discussion within the FDA, and we felt that that would be warranted because it really does show this good-faith effort, that irrespective of outcome, if a plan is made for the fruitful development of a drug, irrespective of outcome, there would be a reward.

DR. BERMAN: But if I could answer that, there is no guarantee that exclusivity is granted, it is that exclusivity will be considered, and there is a board within FDA that looks at that, and as Rick mentioned, the test that has to be met is that the written request, where it is stipulated in the request, has to be satisfied.

DR. PAZDUR: I thought I made it also quite clear. Just because somebody has negative data, that does not mean that we are not going to be looking at the quality of data very carefully. This is not schlock medicine, okay, just send anything in.

It's an effort for a prospective development plan in pediatrics.

DR. D. JOHNSON: I am glad to hear that because we didn't want to see any of that here.

DR. HIRSCHFELD: I would like to just address one step further, Dr. Johnson's question. It is not approval that would occur. This is assuming that there is an approval already for an adult indication.

DR. D. JOHNSON: Right.

DR. HIRSCHFELD: And it would be just an extension onto that. In terms of the diseases that can be extrapolated, we have already issued a list of diseases which we think do not apply, and that may undergo some revision, too.

We look at it, although there may be rare children with some adult type tumors, we have to look at it and the balance in terms of the public health need, and what we are essentially tending to encourage is new information about pediatric oncology that can be applied to future patients and future development of therapeutics.

DR. SCHILSKY: Any other questions from the committee?

[No response.]

DR. PAZDUR: Thank you very much.

DR. SCHILSKY: Thank you, Rick.

We will now go on to the consideration of the Eloxatine application. I will turn it over to the sponsor.

NDA 21-063, Eloxatine (oxaliplatin)

Sanofi Pharmaceuticals, Inc.

Sponsor Presentation

Introduction

MR. MOYER: Good morning.

[Slide.]

On behalf of Sanofi-Synthelabo, I am pleased to introduce oxaliplatin, a novel and significant first-line treatment for advanced colorectal cancer.

Oxaliplatin, as this slide shows, has a unique structure with an oxalato group and a diaminocyclohexane ligand making this represent a new family of platinums, also known as the DAC platinum.

This unique structure provides that both novel preclinical and clinical attributes and of particular interest today is the activity in colorectal cancer. This is different from that observed with cisplatin and carboplatin.

[Slide.]

My name is Mark Moyer and I am the director of Drug Regulatory Affairs for the sponsor Sanofi-Synthelabo. My introduction will be followed by a presentation on the background and efficacy of oxaliplatin by Dr. Mace Rothenberg from Vanderbilt University.

The subsequent presentation will be on the safety,

clinical benefit, and conclusions made by Dr. Daniel Haller from the University of Pennsylvania.

[Slide.]

Oxaliplatin has the brand name of Eloxatine in the United States. It is also known as Eloxatin in Europe. The sponsor is seeking recommendation for approval of Eloxatine as first-line therapy in combination with 5-FU for the treatment of advanced colorectal cancer.

The proposed dosing regimen is outlined on the slide here, consisting of 85 mg/m^2 of oxaliplatin given every two weeks with folinic acid, followed by a bolus and infusion of 5-FU on days 1 and 2 every two weeks.

[Slide.]

This slide denotes the numerous countries where oxaliplatin is already available to patients with colorectal cancer. It also includes those countries where regulatory review and approval process is ongoing.

[Slide.]

This NDA is based on the guideline provided to industry by the Food and Drug Administration in May of 1998, outlining the requirements with evidence to support approval of a new human drug.

This guideline provides for a single adequate and well-controlled trial supported by substantial evidence from other trials.

First, as this slide indicates, Study EFC 2962 is the pivotal trial that demonstrates the safety and efficacy of oxaliplatin with the proposed dosing regimen.

[Slide.]

The supportive trials include EFC 2961, that demonstrates the consistent results of oxaliplatin plus 5-FU in another regimen.

[Slide.]

Independent support of the claim is provided by two trials demonstrating the activity of oxaliplatin plus 5-FU in second-line therapy in EFC 2964 and EFC 2917.

In addition, single agent activity is demonstrated in four monotherapy trials - EFC 2963 and EFC 2960 in first-line therapy, and EFC 3105 and 3106 in second-line therapy.

[Slide.]

Listed here is our panel of distinguished consultants that we have been working with throughout the years. Several of them are here with us this morning to be able to address your specific questions. Many of them have conducted trials not only here in the United States, but also in Europe and representative of the trials that we will be presenting this morning.

Thank you for being with us this morning.

The ODAC panel has several documents before them this morning. First, copies of the overheads were just

provided. In addition, the FDA provided you a list of questions and talking with Dr. Hirschfeld's group within FDA, it was denoted that there is a typographical error on the first table on the first page, in which the p-values for the progression-free survival, between 2962 and 2961 were flip-flopped, so I just bring that to your attention.

A copy of the sponsor's and the FDA's briefing documents were previously sent for your review. The FDA reviewed the submission from the traditional perspective of two adequate and well-controlled trials.

The sponsor has presented information from all the trials in colorectal cancer, the eight primary trials, which were outlined on my slide, and nine additional trials demonstrating consistent results in colorectal cancer.

The pivotal trial results in ESC 2962 are fully supported by the preponderance of evidence from all the trials in colorectal cancer.

We will present the per-protocol analyses in our presentation followed by the conclusion. In addition, exploratory analyses of post-study therapy will be presented since they are appropriate today based on the availability of second-line therapies.

[Slide.]

The ODAC panel has the opportunity to evaluate whether the current state of colorectal therapy and the

evidence presented to you today are appropriate to recommend approval of oxaliplatin.

A positive recommendation would take us one step closer to approval of this important first-line therapy for patients with advanced colorectal cancer, providing yet another significant option for patients.

The sponsor's confidence in this submission is based on three factors. First, the impact on survival and progression-free survival. Second, the tolerability of the proposed dosing regiment. Third, the overwhelming consistency of results from all the colorectal cancer studies, leading to the conclusion that oxaliplatin should be approved for the first-line therapy of advanced colorectal cancer.

[Slide.]

This morning, I am pleased to introduce our presenters. Dr. Mace Rothenberg from Vanderbilt University is a preeminent investigator in colorectal cancer, as well as other GI tumor types. Dr. Rothenberg has treated over 75 patients with oxaliplatin in the United States.

He will be followed by Dr. Daniel Haller from the University of Pennsylvania, also an accomplished investigator in colorectal cancer and other GI tumor types. Dr. Haller has treated over 100 patients with oxaliplatin in the United States, which gives him the unique ability to

present the safety from these studies, as well as his personal experience.

I am now pleased to introduce Dr. Mace Rothenberg.

Mace.

Background and Efficacy

DR. ROTHENBERG: Thank you, Mark.

[Slide.]

My name is Mace Rothenberg from Vanderbilt University. As Mark mentioned, I have had a chance to use oxaliplatin over the last two years, both in the investigational setting using it in Phase I trials, as well as with the compassionate use program.

[Slide.]

Today, I am here to present to you both the background and efficacy in support of this new drug application. My presentation will take the following format. I will give a brief overview of metastatic colorectal cancer and the currently available treatments, and then I will focus on background for oxaliplatin.

The main part of my presentation will be to summarize the efficacy mainly through the pivotal trial known as EFC 2962, and then through supportive trials, which include another first-line, Phase III trial of oxaliplatin with 5-FU and folinic acid known as EFC 2961, combination trials with oxaliplatin, 5-FU, folinic acid in second-line

therapy for patients with relapsed and refractory colorectal cancer, trials 2964 and 2917, and four monotherapy trials, two in front-line therapy and two in patients will relapse disease.

[Slide.]

Colorectal cancer represents a major public health problem for us. This year, more than 130,000 people will be diagnosed with colorectal cancer. Of those, approximately 25 percent, or 32,000 patients, will be diagnosed with Stage IV metastatic incurable colorectal cancer.

But in addition to that, an even greater number, 39,000 people, who are diagnosed with local or locally advanced colorectal cancer, will relapse with metastatic disease, and therefore, the total public health burden this year of having to treat patients with metastatic colorectal cancer is more than 70,000 people.

[Slide.]

Standard practices for treatment of cancer vary from one country to the other. As you know, oxaliplatin was developed primarily in France. In France and most of Europe, 5-FU and folinic acid are administered, not just by bolus regimens, but by bolus and infusion or infusional regimens.

To speak to that point, I would like to go over briefly a trial performed by Dr. Aimery de Gramont and

published in the Journal of Clinical Oncology comparing a European style regimen with a regimen that is more familiar to us in the United States consisting of only bolus 5-FU/ leucovorin.

In this study, patients with metastatic colorectal cancer and no prior treatment for metastatic disease were randomized to a Mayo Clinic daily x 5 bolus schedule or to a bimonthly regimen involving both bolus and infusional 5-FU preceded by infusional folinic acid.

The primary endpoint for this trial was survival, secondary endpoints consisting of response rate, response duration, progression-free survival and safety.

[Slide.]

The results of that trial are shown here. Response rates were more than doubled for the infusional and bolus regimen, 32.6 percent for the de Gramont regimen, 14.4 percent for the Mayo Clinic regimen. This difference was highly significant at the p 0.0004 level.

In addition, progression-free survival was also improved significantly, 6.4 months for the bolus and infusional regimen versus 5.1 months for the bolus daily x 5 regimen, a difference that was significant at the 0.001 level.

In addition, there was a trend towards improved survival with the bolus and infusional regimen, 14.3 months

for the de Gramont regimen versus 13.1 months for the Mayo Clinic regimen.

[Slide.]

This survival difference is depicted through a Kaplan-Meier plot on this slide. The de Gramont regimen, shown here in green on the top, the Mayo Clinic regimen shown here in blue on the bottom. Please keep this curve in mind because we will get back to this later on in my presentation.

[Slide.]

But in addition to a favorable efficacy profile, the bolus and infusional regimen of Dr. de Gramont also had favorable toxicity effects, as well. Grade 3 and 4 toxicities for the bolus and the bolus and infusion regimen are shown here.

As you can see, there was a significantly reduced incidence of serious Grade 3/Grade 4 neutropenia, diarrhea, and mucositis with the bolus and infusional regimen.

In addition, the overall incidence of Grade 3/4 toxicities was 23.9 percent for the Mayo Clinic regimen versus only 11.1 percent for the bolus and infusional regimen, a difference that was highly statistically significant.

So, one can conclude from this trial, and to use FDA's terminology, that the bolus and infusional regimen of

Dr. de Gramont is not inferior to that of the Mayo Clinic bolus daily x 5 regimen. This is the context in which oxaliplatin was developed, and this is the base upon which oxaliplatin was added.

[Slide.]

Oxaliplatin is a platinum, but it is a very different platinum. As Mark mentioned, it is a diaminocyclohexane platinum, and you see the structural differences between oxaliplatin shown here and cis- or carboplatin shown here as they interact with DNA. Their DNA adducts are shown here.

Oxaliplatin adducts are bulkier and more hydrophobic than those produced by cis- or carboplatin. Unlike cis- or carboplatin to which cells are resistant, if they have DNA-mismatch repair deficient cells, oxaliplatin has equivalent activity in DNA-mismatch repair proficient and deficient cells in vitro.

There is preclinical activity in colorectal cancer cell lines, and I will show you that in just a moment. Also, there is preclinical synergy between oxaliplatin, 5-FU and folinic acid.

[Slide.]

This is a representation of the NCI's human tumor cell line screen, and this is the pattern of activity. What this line represents here is the mean IC50 for each of these

drugs when tested against the 50 human tumor cell lines in that screen.

The bars that go to the left, and depicted here in orange, mean that against these colon cancer cell lines, that there is a lower effect than the median effect versus platin against all of these 50 cancer cell lines.

So, as you can see, the profile, the pattern for both cis- and carboplatin suggest that this is not a very active tumor target for these drugs.

In contrast, oxaliplatin has bars going to the right of this mean effect in six of the eight cancer cell lines meaning that it has greater than median effect in colon cancer cell lines.

I would also like to point out that this axis is actually a logarithmic axis, which means that in these cell lines, there is 10- to 100-fold greater effect in these colorectal cancer cell lines than in the average cells in the cancer cell line.

When we look at patterns using a Spearman rank correlation coefficient, as you might imagine, there is a very high degree of correlation in the patterns of activity for cis- and carboplatin and a very low correlation in patterns of activity for oxaliplatin against either cis- or carboplatin, again underlying the fact that this is a very different platinum from the ones we currently have

available.

[Slide.]

Dr. Fischel and colleagues in 1998 published results of a series of in vitro studies in which they studied the interactions between 5-FU and oxaliplatin. What they found was that in 78 percent of situations tested, which included four human colorectal cancer cell lines, three different sequences of administration, and three different durations of drug exposure, oxaliplatin enhanced 5-FU with or without folinic acid cytotoxicity.

[Slide.]

Turning now to clinical results, there were two, Phase I clinical trials performed with oxaliplatin. Both of these were performed using a once-every-3-week schedule, and both found dose-limiting toxicities in this very close range of 180 to 200 mg/m^2. The dose-limiting toxicity was a cumulative, reversible peripheral neuropathy.

From these studies, the recommended Phase II dose was 130 mg/m^2 every three weeks. As you might recall, the bolus and infusional regimen of 5-FU/folinic acid of Dr. de Gramont is given every two weeks.

So, in an effort to maintain equivalent dose intensity, the dose of oxaliplatin used with the de Gramont regimen is 85 mg/m^2.

[Slide.]

I would now like to turn my attention to the pivotal trial known as EFC 2962.

[Slide.]

This is a randomized, controlled, Phase III trial that was performed in patients with metastatic colorectal cancer who were receiving front-line treatment for the metastatic disease.

It was a multi-national, multi-center trial performed in nine countries in 37 centers. Enrollment was conducted between August 1995 and July of 1997.

[Slide.]

The trial design is shown on this slide. Patients with metastatic colorectal cancer were assigned treatment arms using a randomization with minimization method for center, performance status, and number of metastatic sites.

The control arm on this trial was the de Gramont regimen of 5-FU/folinic acid, the exact same one that was used in the French intergroup trial that I showed earlier.

The investigational arm was that same 5-FU/folinic acid regimen to which oxaliplatin was added at a dose of 85 mg/m^2 on day 1 every two weeks.

[Slide.]

The primary endpoint of this trial was progression-free survival. Again, this was performed in Europe where progression-free survival is often the primary

endpoint for pivotal trials since it is felt to be most reflective of the effect of front-line therapy.

The secondary endpoints included response rate, and these response rates that I will report were those that were determined by an independent review and only those in which a confirmatory scan was obtained four weeks afterwards.

Other secondary endpoints included overall survival and safety.

[Slide.]

Data were analyzed in an intent-to-treat basis, so all randomized patients were included in the analysis. There was a planned adjustment for prospective prognostic factors.

Data cut-off dates for safety and primary efficacy were January 1998, for overall survival was July 1998.

[Slide.]

The trial was designed to enroll 400 patients, and actually, 420 patients were enrolled, 210 patients on each arm. Follow-up for a given patient was not to exceed 35 months, so it would allow a specific date to be used as a data-locking date. This also represented five times the median progression-free survival that was expected on the control arm.

The null hypothesis was that there was no

difference in progression-free survival. The alternative hypothesis was that there would be a three-month improvement in median progression-free survival from 7 to 10 months, representing a 43 percent relative improvement in progression-free survival, a difference that was felt to be clinically meaningful by the clinicians.

The trial was designed to have a two-sided test for significance at the 0.05 level with an 80 percent power to detect this difference.

There was one planned interim analysis with an early stopping rule based on response.

[Slide.]

There were 14 prospectively identified prognostic factors. They were prospectively selected and data on these characteristics was prospectively collected.

These included center, age, gender, WHO performance status, presence or absence of liver metastases, the Astler-Coller's stage at diagnosis originally, number of organs involved with metastases, primary site of the tumor, colon or rectum, whether they received prior adjuvant chemotherapy or radiotherapy, SGOT, SGPT, alkaline phosphatase, and creatinine.

[Slide.]

The inclusion criteria are listed on this slide, and this included histologically proven adenocarcinoma of

the colon or rectum. The patient must have had metastatic disease that was considered surgically inoperable.

The patient may have received no prior immunotherapy or chemotherapy for metastatic disease, but they may have received prior adjuvant therapy as long as that adjuvant therapy was completed at least six months prior to study entry.

The patient had to have at least one bi-dimensionally measurable lesion measuring at least 2 cm in greatest dimension on MRI or CT scan. WHO performance status less than or equal to 2. Adequate chemistries and bone marrow reserve, and age between 18 and 75.

[Slide.]

On this slide and the next slide, the baseline patient characteristics are shown. Although there was good balance between the two treatment arms, note that the numbers are not identical.

[Slide.]

I would particularly point out the alkaline phosphatase here, as well as the particular organs that are involved and the number of organs involved. This is an important point that I will come back to later, since some of these baseline characteristics are significant predictors of outcome in patients with advanced colorectal cancer.

[Slide.]

The primary endpoint of the trial was progression-free survival, and that is shown on this slide. Progression-free survival was increased from 5.9 months on the control arm to 8.1 months on the oxaliplatin arm. Hazard ratio was 0.67, and this represented a 33 percent reduction in the risk of progression for patients who received front-line oxaliplatin. This difference was significant at the 0.0003 level.

[Slide.]

Secondary objectives included response rate. Here again, the objective response rate was also improved by the addition of oxaliplatin, from 21.9 percent for the 5-FU/folinic acid control arm, to 49 percent on the oxaliplatin/5-FU/folinic acid arm. This difference was significant at the 0.001 level, chi-square, 2-tailed test.

[Slide.]

This slide shows the overall survival which is unadjusted for baseline differences in prognostic factors. Median survival for the control arm was 14.7 months, for the oxaliplatin arm was 15.9 months.

The hazard ratio was 0.83 representing a 17 percent reduction in the risk of death for patients who received front-line oxaliplatin. The p-value for this difference was 0.13.

However, the unadjusted survival curve does not

tell the whole story. A per-protocol analysis was performed on those 14 baseline characteristics that I showed earlier to see what extent, if any, these may have influenced this result.

[Slide.]

In a Cox proportional hazards analysis, three baseline characteristics came out as being significant predictors for outcome. These included WHO performance status, alkaline phosphatase, and number of organs involved. When these baseline differences were taken into account in this analysis, now the treatment arm became a significant predictor for survival. That is shown on the next slide.

[Slide.]

Here is that same Kaplan-Meier overall survival curve, but now it is adjusted for baseline imbalances and performance status, number of organs involved, and baseline alkaline phosphatase.

The hazard ratio has gone from 0.83 to 0.70 and now representing a 30 percent reduction in risk of death for patients who received front-line oxaliplatin, and using the Cox model test statistic, this difference is significant.

[Slide.]

This Kaplan-Meier overall survival curve represents the de Gramont regimen 5-FU/folinic acid published in JCO in 1997 that I showed to you earlier.

The question that arises is whether advances that are made in clinical trials are more apparent than real. In other words, did the control arm in this study, 2962, the one that I just showed, perform worse in this trial than it did when it was the investigational arm in the previous study.

So, here, as a baseline, I show you the results of the 1997 published trial using just 5-FU/folinic acid either by the Mayo Clinic regimen or the de Gramont regimen.

Now, when we show the control arm of 2962, the same de Gramont 5-FU/folinic acid regimen, we see that it did not perform worse in this trial, it actually performed identically with the way it had previously.

Now, when we take a look at the oxaliplatin arm of 2962, we see that that performed here, and it shows you the oxaliplatin control arm, the two de Gramont 5-FU arms, and the 5-FU/folinic acid regimen of the Mayo Clinic bolus x 5.

So, the key point here is that the superiority of the oxaliplatin arm of 2962 did not occur because of underperformance of the control arm, but because of the added benefit of oxaliplatin to 5-FU and folinic acid.

[Slide.]

So, what we can say from the results of the pivotal trial 2962 is that the addition of oxaliplatin results in significant improvement in survival with a 30

percent reduction risk of death after protocol-defined adjustments for baseline imbalances and prognostic factors, that it provides a progression-free survival advantage with a 33 percent reduction in risk of progression to that achieved with just 5-FU/folinic acid, and also has an advantage in terms of response rate, with more than 2.2-fold increase in confirmed objective response rates compared to the control arm.

[Slide.]

During the conduct of this study, between the years 1995 and 1997, data emerged on the beneficial impact of second-line chemotherapy with irinotecan on the improvement in survival in patients with colorectal cancer.

Therefore, it was of interest to us to examine what impact, if any, the use of second-line chemotherapy might have had on the outcome of this trial.

In a retrospective analysis, we found that 15 percent of patients who were randomized to the control arm received oxaliplatin afterwards, 10 percent received CPT-11 afterwards, 8 percent received both, representing a third of patients receiving second or subsequent treatment with oxaliplatin and/or CPT-11.

An equivalent percentage of patients received second-line or third-line chemotherapy on the investigational arm, as well, although this primarily

represented CPT-11.

[Slide.]

Here, the results of 2962 are depicted with the results, with the patients who received second-line treatment with irinotecan, oxaliplatin, or both, censored at the time of initiation of that second-line therapy. This was done in an attempt to try and remove the confounding factor of what influence, if any, second-line therapy had on survival.

In this exploratory analysis, the hazard ratio was 0.72 in favor of the oxaliplatin front-line treatment compared to the 5-FU/folinic acid treatment arm, representing a 28 percent reduction in risk of death for patients who got front-line oxaliplatin when the confounding effects of second- or third-line therapy with CPT-11 or oxaliplatin were taken into account. This difference was significant with a log-rank p-value of 0.03.

[Slide.]

I will now turn my attention to the first of several supporting trials. This is EFC 2961, which was the other Phase III front-line regimen in colorectal cancer.

[Slide.]

Patients with metastatic colorectal cancer and no prior treatment for first-line metastatic disease and at least six months since prior adjuvant therapy, adequate WHO

performance status, and age below 75 were randomized once again to a 5-FU/folinic acid control arm versus that same treatment to which oxaliplatin was added. In this case, it was a chronomodulated method of administering 5-FU and folinic acid.

[Slide.]

The primary endpoint of this trial was objective response rate, and those results are shown here. There was a 12 percent objective response rate for the control arm versus a 34 percent response rate for patients who received oxaliplatin as part of front-line therapy.

You may note that these numbers are slightly lower than those I showed to you for 2962, and the reason for that is very likely that response evaluation, instead of being every eight weeks, was every nine weeks, but more importantly, instead of a confirmatory scan being reported or performed at four weeks, it was performed at nine weeks. Nevertheless, there was a near tripling of the objective response rate in favor of oxaliplatin treatment front-line.

[Slide.]

The secondary endpoint of this trial was progression-free survival, and once again, oxaliplatin is shown on the top, the control arm of 5-FU/folinic acid shown on the bottom.

The median progression-free survival of 4.2 months

in the control arm was nearly doubled in the oxaliplatin 5-FU/folinic acid arm. Hazard ratio for progression was 0.74, representing a 26 percent reduction in the risk of progression for those people who got front-line oxaliplatin, a difference that was significant at the 0.05 level.

[Slide.]

Another secondary endpoint was overall survival. Here, the results are much tighter - 5-FU control arm, median survival of 19.2 months; oxaliplatin, of 17.4 months. Hazard ratio of 0.11, log-rank, p-value of 0.58.

I should also point out that these results on both 2961 for survival and 2962 are among the longest ever reported for trials done in front-line treatment of patients with metastatic colorectal cancer.

This trial took an aggressive approach to patients with advanced colorectal cancer, and patients who failed to respond to front-line therapy were rapidly switched to salvage treatment.

[Slide.]

The second-line approaches are shown here. So, this is after patients finished their protocol-mandated treatment, they were then allowed to be treated per the discretion of the treating physician, and as you can see, nearly two-thirds of patients who were assigned to the control arm then received oxaliplatin second-line.

Twenty-six percent received CPT-11, and more than 80 percent received some chemotherapy on both arms, but in addition, patients who were placed on this trial had to have surgically inoperable metastatic disease at the time of randomization.

The group performing the study took a very aggressive approach to trying to perform salvage surgery to resect any residual disease if possible, because it was felt that that had beneficial influence on survival. As you can see, that is reflected in the fact that a third of patients on both arms were able to undergo resections for potential cure after entering the trial having inoperable disease.

[Slide.]

It was again of interest to us to try and evaluate what influence, if any, this second-line treatment approach had on the outcome in this study. In this adjusted Kaplan-Meier curve, we have taken into account post-study oxaliplatin, CPT-11, or surgery and censored people at the time that they received that salvage therapy.

When you do that, again, the oxaliplatin curve now splays a little bit more from the 5-FU curve, hazard ratio is now 0.58 indicating a 42 percent reduction in the risk of death in patients treated with front-line oxaliplatin, a difference that approached, but did not reach statistical significance, but I should remind you that this was a

secondary endpoint, this is a subset analysis, and this is a trial that had 100 patients on each arm, so therefore, we must make these analyses with some caution.

[Slide.]

What I would like to point out now is the consistency of results between 2961 and 2962. I think that that is quite notable for both overall survival and progression-free survival, the results for the oxaliplatin arms in both trials is very consistent in terms of overall survival and progression-free survival.

I would also like to remind you that the progression-free survival here is 8.1 and 8.3 months. That also is among the longest ever reported for front-line regimens for the treatment of metastatic colorectal cancer.

[Slide.]

Next, I would like to present the use of the 5-FU/folinic acid/oxaliplatin combination in the second-line treatment of patients with recurrent or refractory colorectal cancer.

[Slide.]

In the study known as 2964, patients who had disease progression within six months of receiving prior 5-FU, and up to two prior 5-FU-based regimens, could have received either that same bimonthly de Gramont regimen including oxaliplatin/5-FU/folinic acid or a modification of

that also every two weeks.

[Slide.]

The results of this combination when used in second-line therapy indicated a response rate of approximately 20 percent, but our experience with irinotecan also taught us that it is not just those patients who have objective responses who benefit because these people all had progression of their disease to become eligible. Even tumor stabilization could be of benefit, and therefore, we looked at that, as well, and found approximately 50 percent of patients had tumor stabilization on these regimens.

Progression-free survival was 4.6 to 5.3 months, and overall survival was 10 to 11 months. This data and the data that I will show you next are very consistent with those obtained with second-line irinotecan.

[Slide.]

The second trial is 2917, very similar, but not identical patient population. Patients must have demonstrated progression within two months of prior 5-FU, up to one prior to 5-FU-based regimen, but here, the use of the 5-FU was actually restricted, so that the patients must receive the 5-FU in the exact same fashion on which they were progressing, and the only change made was the addition of oxaliplatin.

This study design removed the influence, whatever

influence it may have had, of changing the 5-FU treatment regimen from bolus to infusion or from one schedule to another, so this just looks at the addition of oxaliplatin in patients with recurrent colorectal cancer.

[Slide.]

Here, the response rates are slightly lower, 7 to 13 percent, but again, 50 percent stable disease rate, 4 to 4 1/2 month progression-free survival, and overall survival 10 to 11 months, again very consistent with the previous trial.

[Slide.]

I would like to conclude the presentation with the rapid review of the oxaliplatin monotherapy studies, two of which were done in front-line therapy, two of which were done in relapsed patients.

[Slide.]

In patients who had previously received no treatment for metastatic colorectal cancer, oxaliplatin as a single agent had a response rate of 12 to 27 percent, progression-free survival of four months, and overall survival in excess of one year.

When used in previously treated patients, the response rate was somewhat lower, 7.8 to 10.3 percent, and were dated as available overall survival of 8.2 months.

[Slide.]

So, to summarize my portion of the presentation, I think that the important points are the consistent results of the oxaliplatin/5-FU/folinic acid regimen in front-line therapy. That is shown here with experience including more than 300 patients, progression-free survival 8.1/8.3 months. Overall survival 15.9/17.4 months, and one year survival rates of almost 70 percent.

[Slide.]

Oxaliplatin also has activity in relapsed or refractory patients with colorectal cancer consistent with standards. This is shown in the results from 2964 and 2917 with progression-free survival in the four to five month range, and overall survival of 10.1 to 11.1 months.

[Slide.]

So, overall, what can we conclude from this portion of the presentation? Well, I feel that oxaliplatin has consistent and reproducible activity in patients with metastatic colorectal cancer, and that activity appears to be greatest when oxaliplatin is used in combination with 5-FU/folinic acid as front-line therapy.

I would now like to turn the presentation over to Dr. Dan Haller of the University of Pennsylvania, who will present a summary of the safety of oxaliplatin and conclude this presentation.

Safety, Clinical Benefit, and Conclusions

DR. HALLER: Good morning.

[Slide.]

My name is Dan Haller and I am presenting the safety data for oxaliplatin. As Mark Moyer told you, I am a medical oncologist at the University of Pennsylvania Cancer Center, and I have a long-standing clinical interest in gastrointestinal oncology, 25 years of clinical experience in taking care of patients with colorectal cancer, and with a personal experience of treating over 100 patients with oxaliplatin therapy for refractory colorectal cancer.

[Slide.]

The safety presentation will describe the qualitative toxicities of oxaliplatin used as monotherapy in the first-line treatment of colorectal cancer, as well as the safety profile of oxaliplatin and 5-FU and folinic acid from the primary pivotal trial EFC 2962.

In addition to some typical chemotherapy-related toxicities, oxaliplatin therapy is often associated with neurotoxicities that are relatively unique to this drug, and these will be described in detail.

I will also present available evidence of clinical benefit including time-to-treatment failure as a surrogate of both safety and efficacy.

Although approval is being sought for combination chemotherapy with 5-FU and folinic acid, single agent trials

have been completed which delineate those side effects attributable to oxaliplatin.

[Slide.]

The data for the toxicity profile of oxaliplatin in monotherapy is derived from two trials of previously untreated colorectal cancer patients at a dose of 130 mg/m^2 every three weeks.

WHO Grade 3 to 4 nausea and vomiting was observed in 11 to 13 percent of patients and diarrhea in less than 5 percent. Significant Grade 3 to 4 myelosuppression was seen in 10 percent or less of patients, and characteristic paresthesias were observed in approximately 20 percent. Patients did not develop clinically significant hair loss, nephrotoxicity, or ototoxicity.

[Slide.]

The primary basis for safety labeling, however, was in the pivotal trial EFC 2962, in which oxaliplatin is given in combination with 5-FU and folinic acid.

In this trial, oxaliplatin was administered at a dose of 85 mg/m^2 every 2 weeks, and the primary safety data will come from the dose schedule used in this study. However, these safety data are representative of the composite safety profile from all of the trials included in the ODAC briefing document.

The safety profile from EFC 2962 is derived from

more than 5,000 cycles of therapy and 417 patients randomized to infusional and bolus 5-FU and folinic acid alone or to the same therapy with oxaliplatin.

The median number of cycles was 11 in the 5-FU and folinic acid arm and 12 in the combination arm with a range of up to 40 and 35 cycles respectively.

Gastrointestinal toxicities are frequently observed in patients receiving 5-FU-based chemotherapy with commonly accepted Grade 3 to 4 side effects in 20 to 40 percent of patients treated with standard bolus regimens.

[Slide.]

In EFC 2962, gastrointestinal toxicities were relatively uncommon. Independent of the treatment arm, by patient, the occurrence at any time during therapy is Grade 3 to 4 nausea or vomiting, for oxaliplatin and 5-FU was somewhat higher than for 5-FU and folinic acid alone, but not significantly.

Both diarrhea and stomatitis were significantly more common with combination therapy, but still considerably less than that reported from comparator arms of trials using bolus 5-FU and folinic acid.

When the same data are analyzed by cycle, similar trends toward a modest increase in gastrointestinal toxicity are observed, but the incidence of even the most frequent toxicity, diarrhea, was extremely low in any given cycle.

Hematologic toxicity with oxaliplatin has also been described including neutropenia and thrombocytopenia. For the combination of oxaliplatin and 5-FU and folinic acid in the pivotal trial, a significant trend for Grade 3 to 4 neutropenia was documented. Clinically, however, this rarely resulted in neutropenic fever with no difference between the treatment arms.

Significant anemia or thrombocytopenia were uncommon and the incidence of these side effects was not increased with combination chemotherapy. Again, when analyzed by cycle, the risk of developing clinically relevant myelosuppression during any treatment cycle was 6 percent or less with extremely low rates associated with either treatment.

Therefore, although laboratory evidence exists for increased myelosuppression when oxaliplatin is added to 5-FU and folinic acid, patients rarely suffered clinically relevant adverse consequences. The same is true for laboratory measures of other organ system toxicities.

[Slide.]

Significant hepatic or renal dysfunction was uncommonly observed in EFC 2962 whether analyzed by patient or by cycle. There were no differences between the treatment arms.

The tolerance of the treatment regimen is based

not only on innate properties of the individual drugs, but also on the dose and schedule modifications that are instituted during therapy.

[Slide.]

This is, in part, demonstrated in the exposure of patients to the drugs in the two arms of the pivotal trial. In the 5-FU and folinic acid arm, 89 percent of ideal dose was administered. When oxaliplatin was added biweekly, toxicities, typically gastrointestinal and hematologic, led to dose reductions in both drugs, so that somewhat less 5-FU was administered in the combination arm.

When analyzed by patient and by dose, reductions and delays were significantly more common in the combination arm. By cycle, approximately one-third of treatment courses of oxaliplatin with 5-FU and folinic acid required dose reduction or delay compared with roughly 10 percent in the 5-FU and folinic acid control arm.

[Slide.]

The data have been analyzed to explore the reasons for dose reductions or delays in EFC 2962. When analyzed for dose reduction, neurotoxicity resulted in dose reductions only of oxaliplatin in 66 patients. Hematologic toxicity required dose reduction in both 5-FU and oxaliplatin in 71 patients, significantly more than the 10 patients in the control arm.

Less commonly, gastrointestinal toxicity required dose reductions in 5-FU or oxaliplatin. Overall, dose reductions were more common with combination therapy typically for neurotoxity or myelosuppression.

[Slide.]

Nearly twice as many cycles were delayed in the combination arm compared to the control arm. Most often this was for personal reasons, such as vacations or other nontreatment-related factors. Increased myelosuppression from the combination resulted in treatment delays more often in the infusional fluorouracil control arm which, by itself, results in little hematologic toxicity.

Treatment delays for other toxicity including neurotoxity alone were extremely uncommon. Taken together, appropriate dose reduction and treatment delays result in a combination regimen that is both tolerable and effective.

[Slide.]

Treatment-related mortality has been a rare event in oxaliplatin trials. For the pivotal and supporting trials, EFC 2962 and 2961, 4 deaths were observed in 616 patients, less than 1 percent overall. These data are consistent with the low rates observed in the data presented in the briefing document for the 8 primary studies in colorectal cancer and for the 33 total studies presented in which the combined treatment-related mortality was less than

1 percent of more than 2,700 patients.

These data compare favorably to series of patients treated with single agent fluorouracil therapy.

The development of oxaliplatin has been associated with the evolution of scales to describe qualitatively and quantitatively the neurotoxicity associated with this drug. It is therefore important to briefly review the neurotoxicity grading scales used in the pivotal trial and in the supporting studies.

[Slide.]

At the time the EFC 2962 was accruing patients, the NCI common toxicity criteria did not address the duration of sensory neuropathy, and the highest grade assigned was Level 3.

To better capture the nature of oxaliplatin neurotoxicity, EFC 2962 also employed a trial-specific scale that assigned a grade according to severity of paresthesias and duration with the highest grade given to those patients who had functional impairment persisting between treatment cycles. In addition, grading from none to severe was also performed for patients developing paresthesias of the pharyngeal/laryngeal area.

It is important to describe clinically the neurotoxicities that are associated with oxaliplatin therapy as you heard earlier. Some are similar to those seen with

other approved chemotherapy drugs, such as the vinca alkaloids, taxons, and other platinate compounds.

Other manifestations of neurotoxicity appear relatively unique to this compound. My own experience in administering more than 700 cycles of this drug has allowed me to better understand the nature of the neurotoxicity.

[Slide.]

Cold-related paresthesias comprise the most commonly observed characteristic neuropathy. This may occur in the distal extremities or in the pharyngo-laryngeal area and is typically mild, occurring initially within hours of the infusion.

Characteristically, this toxicity is transient, lasting three to five days after the infusion. Patient frequently describe the sensation as being similar to touching dry ice with the fingers or swallowing ice crystals.

Much less common is the constellation of symptoms termed the pharyngo-laryngeal syndrome, which describes dysesthesias of the throat resulting in a subjective sensation of dysphasia or dyspnea. When this occurs, it is always considered Grade 3. Therefore, cold-related paresthesias are common, but they are rarely severe.

[Slide.]

When analyzed by the trial-specific neurotoxicity

scale in the pivotal trial EFC 2962 and for two supporting trials, cold-related paresthesias of the distal extremities of any grade were observed in 68 percent of patients in the pivotal trial and 78 percent in the supporting trials. However, Grade 3, persistent paresthesias or the pharyngo-laryngeal syndrome were much less common, the latter occurring in less than 1 percent of patients in the pivotal trial.

As with other chemotherapy-related toxicities, optimal clinical management affects the ability of the patient to receive effective therapy.

[Slide.]

Patients must be made aware of the likelihood of transient cold-related paresthesias and advised to avoid cold drinks or foods within a few days after therapy. In the winter, gloves may be advisable. Although not typically required with infusional and bolus therapy as used in this trial of 5-FU, ice chips should be avoided during treatment.

Both the patient and the physician should be aware of the rare occurrence of the pharyngo-laryngeal syndrome. If clinically indicated, airway obstruction can be readily ruled out by simple clinical examination and reassurance and anxiolytics may be administered as needed.

On subsequent cycles, prolongation of the infusion beyond two hours may reduce the likelihood of recurrence.

[Slide.]

Both patients and physicians should also be aware of a cumulative neurotoxicity which occurs less commonly in patients who are receiving prolonged therapy.

Cumulative sensory neuropathy persisting between cycles may progress to functional impairment. Clinically, this manifest is difficulty in fine finger movements, such as difficulty in small buttons or in differentiating coins. This toxicity occurs only rarely in patients before they have received a total cumulative dose of 850 mg/m^2 or approximately 10 cycles.

Limited data in patients with long follow-up after therapy suggests that this toxicity is reversible upon cessation of treatment.

[Slide.]

To better quantify the likelihood of developing such toxicity, the totality of reported Grade 3 neurotoxicity upon the pivotal trial have been summarized. When all Grade 3 neurosensory toxicities, as measured by the NCI scale or persistent Grade 3 paresthesias by the trial-specific scale were analyzed, the risk of a patient ever developing clinically significant functional impairment secondary to neurotoxicity is less than 20 percent. This risk appears similar whether captured by the NCI scale or the trial-specific scale.

By comparison, the risk of developing Grade 3 neurotoxity from a recently reported trial of platinum and taxol combinations for non-small-cell lung cancer ranged from 23 to 40 percent.

From the standpoint of both the clinician and the patient, understanding of the relationship between Grade 3 neurotoxicity and treatment duration is important.

[Slide.]

This slide portrays the likelihood of achieving objective response compared to the time course associated with the onset of cumulative Grade 3 neurotoxicity. By eight cycles, most responding patients will have been identified, but few patients will have developed Grade 3 neurotoxicity by either the NCI or the trial-specific scale.

These characteristics mean that patients who progress early will rarely experience significant neurotoxicity. Also, responding and surviving patients have the opportunity to evaluate and discuss their toxicities with their physician and to modify unacceptable toxicity with schedule and dose modifications.

[Slide.]

To further explore the impact of cumulative sensory neuropathy on the clinical status of patients, the performance status of those patients with Grade 3 neurotoxicity at their final cycle of treatment was compared

to those patients without significant neurotoxicity.

As you can see, there were no differences for any performance status in the proportion of patients with or without Grade 3 neurotoxicity. This indicates that the occurrence of even the most severe neurotoxicity did not substantially affect patient's ability, continued to lead a normal or near normal lifestyle as measured by one of the most accepted global scales of clinical status.

[Slide.]

In summary, the safety data for the addition of oxaliplatin to 5-FU and folinic acid shows a modest increase in diarrhea and stomatitis, rare febrile complications in spite of a significant increase in neutropenia, rare toxic death with the proposed dosing regimen, and manageable acute neurosensory symptoms and reversible cumulative paresthesias uncommonly interfering with routine clinical management or effective therapy.

[Slide.]

To enrich the safety and efficacy presentation, two measures of patient benefit and tolerability are now presented from the pivotal trial - time to treatment failure by the SWOG criteria, which includes time to progression and death, or discontinuation of treatment for any cause, and the reasons for withdrawal during treatment.

[Slide.]

When all causes of treatment failure were included, combination therapy with oxaliplatin and 5-FU and folinic acid was superior to 5-FU and folinic acid alone whether measured at specific time points or with the log-rank test with a p-value of 0.003.

[Slide.]

To further elucidate why these differences were observed, the reasons for treatment failure were identified. In the pivotal trial, the most common reason for discontinuing treatment was progressive disease, which was more common with 5-FU and folinic acid alone, 65 versus 49 percent for combination therapy.

Withdrawal for adverse events or refusal for any cause were somewhat more common with the combination therapy, but other causes or death were similar between the two arms.

[Slide.]

To conclude the safety presentation, I would like to emphasize two points. First, the toxicity of the 5-FU/folinic acid regimen used in EFC 2962, and proposed for labeling, is by itself considerably less toxic than typical bolus 5-FU regimens used in the United States. Even when oxaliplatin is added in the proposed dosing regimen, the combination is extremely well tolerated.

Second, when toxicities do occur, they are

predictable, manageable, and toxicity rarely limits effective treatment.

[Slide.]

In closing, I would now like to briefly review the efficacy data constituting the basis for approval for the combination of oxaliplatin and 5-FU and folinic acid in the first-line therapy of colorectal cancer.

[Slide.]

From the pivotal trial, EFC 2962, efficacy has been established. Both response rate and progression-free survival were significantly better for the combination of oxaliplatin and 5-FU and folinic acid than for 5-FU and folinic acid alone in first-line treatment for colorectal cancer.

In addition, overall survival was significantly improved as measured by the adjusted Kaplan-Meier statistics.

[Slide.]

There has also been consistent evidence for combination therapy with oxaliplatin and 5-FU and folinic acid shown in another first-line trial, 2961. When compared, the response rates, progression-free overall, and one-year survivals for the combination of oxaliplatin and 5-FU and folinic acid are remarkably similar between the two trials.

[Slide.]

From other supportive trials, the combination of oxaliplatin and 5-FU and folinic acid has shown clinical activity in patients with relapsed or refractory colorectal cancer, which I have had the opportunity to observe in my own practice.

Oxaliplatin has demonstrated single agent activity in patients with previously untreated advanced colorectal cancer, and finally, oxaliplatin has also shown single agent activity when used in patients with relapsed or refractory colorectal cancer.

[Slide.]

Based on these efficacy and safety data, we conclude that the combination of oxaliplatin and 5-FU and folinic acid should be approved for the first-line treatment of colorectal cancer.

Thank you.

Questions from the Committee

MR. MOYER: Any questions from the panel for our presenters? We also have with us Dr. Jean Vialle [ph], a medical oncologist from Sanofi-Synthelabo, who is our project director for Clinical Research, and Dr. Bill John, also a medical oncologist from Eli Lilly Company, who is the project director for Clinical Research from our partner, and Dr. Robert Bigelow, our statistician for the project.

DR. SCHILSKY: Thank you. I believe there may be one or two questions from the committee.

Dr. Kelsen.

DR. KELSEN: In 2962, in the pivotal trial, the initial survival analysis did not show a statistical benefit, so you elected to do an adjusted survival analysis, and you focused on alkaline phosphatase, performance status, and the number of organs involved in your multivariate analysis as predicting outcome.

My first question is why you chose alkaline phosphatase since there are many other laboratory values that you might have looked at, and my second question is as you look at the raw data, the number of patients with PS2 is identical between the two arms, 11 percent.

The number of organs involved is actually slightly worse for the comparator arm than it is for the experimental arm, and so is the bulk. I don't know if you can answer this statistically, but is the bulk of the improved survival seen for the adjusted analysis because of the discrepancy in alkaline phosphatase in the experimental arm compared to the comparator arm, since that makes up the bulk of the advantage that you saw.

MR. MOYER: So, your question is regarding the adjustments made that were per protocol on alkaline phosphatase was actually first based in a meeting with

Rougier in November of '96, in which we were informed that that was a significant factor.

I will turn it over to Dr. Mace Rothenberg to address how that came about.

DR. ROTHENBERG: The first question you asked regarded alkaline phosphatase, how was that selected as one of the baseline characteristics, and actually, it is one of several different indicators of tumor burden and involvement of the liver, and this is something that has been recognized for a number of years in trials with 5-FU/leucovorin with CPT-11 and with oxaliplatin, and we do have some back-up slides to address that.

[Slide.]

In 1995, Philippe Rougier published in the British Journal of Surgery an analysis of a trial that was looking at early surgical intervention, patients with advanced colorectal cancer.

He looked at a number of possible prognostic factors in a very large number of patients. Alkaline phosphatase did turn out to be a very significant prognostic factor for survival with a risk ratio of 1.6.

Now, to follow forward with this, this same parameter has been applied in the two pivotal trials for second-line treatment with irinotecan published in Lancet 1998 by Philippe Rougier and David Cunningham. Looking at

baseline alkaline phosphatase in each of those trials, risk ratios again were between 1.5 and 2.7 using baseline alkaline phosphatase as the parameter, all of which were statistically significant predictors of survival.

[Slide.]

Then, when we look at the other trials that we just presented, the French intergroup trial published in 1997, the baseline alkaline phosphatase elevations were associated with a risk ratio more than twice those patients who had normal alkaline phosphatase.

In the other Phase III trial that I presented, EFC 2961, baseline alkaline phosphatase was again a risk factor associated with a 50 percent increased risk of death to those patients in whom it was elevated.

So, I think that there is a very consistent picture that emerges here over the last five years indicating that in patients who have elevated alkaline phosphatase, that in and of itself is a poor prognostic factor for survival.

Does that answer your first question?

DR. KELSEN: There are a number of other laboratory tests that are based on the same analysis.

DR. SCHILSKY: If I could just follow up on that, on your comment. So, if alkaline phosphatase is such an important prognostic factor, why was the trial not

stratified in advance for alkaline phosphatase?

DR. ROTHENBERG: That is a question that I could turn over in terms of the people who designed that trial.

MR. MOYER: My understanding is that the study was designed with the minimization technique for the factors that were listed on Dr. Rothenberg's slide.

It was in November of '96, the meeting with Dr. Rougier and the steering committee, of which there was in the per-protocol, it stated that there was collected alkaline phosphatase and the other 14 prognostic factors were captured, and the protocol specified that accidental bias would be adjusted for in the final analysis.

The log-rank was the primary analysis, but that there would be an analysis for accidental bias. That was submitted to the FDA. We had an actual meeting with the FDA because this study was started before the sponsor ever took over.

All these studies were conducted under European guidance and regulations, not under the U.S. IND, and we had a meeting with the FDA in October of 1998 in which they had asked for the final analysis plan, which was signed off in December of '97--I am sorry, it was October '97 we had the meeting. We had signed off in December '97, the final analysis plan for survival being that was not a primary endpoint which included, that we were just going to look at

only the prognostic factors that were collected, no other additional factors, and that was submitted in February 1998, six months prior to the July cut-off for the final survival analysis.

DR. KELSEN: Could you just go over the answer to the question as to is the bulk of the benefit that is seen on the basis of the adjusted survival due to the discrepancy in alkaline phosphatase, is that what shifts this over, or can you not do that?

DR. ROTHENBERG: Let me address that because that is also something that we thought about a lot, and this has to do with the issue of alkaline phosphatase and baseline imbalances of prognostic factors.

If I could have those series of slides.

[Slide.]

This shows the original unadjusted overall survival curve showing oxaliplatin and 5-FU/folinic acid.

[Slide.]

In the Cox proportional hazard analysis, on the 14 prospectively identified prognostic factors, WHO performance status, alkaline phosphatase, the number of organs involved turned out to be significant prognostic factors in and of themselves. When those imbalances were taken into account, then, the treatment arm became a significant, also prognostic factor for survival.

[Slide.]

When we adjusted that for the Kaplan-Meier overall survival curve, that is shown here, hazard ratio of 0.7, Cox model p-value of 0.01.

[Slide.]

Now, the issue here was, as you point out, there are some very subtle differences when we look at number of organs involved, 40 percent had one, 43 percent had one here, and that was actually in favor of the oxaliplatin arm.

When we looked at alkaline phosphatase, the differences were very subtle and none of these were statistically significant, so the question became how did these very subtle numerical differences come out as significant prognostic factors in the Cox proportional hazard model.

In order to understand that small numerical differences can actually be significant if the prognostic factor is a strong one, I could give you the example of a tug of war where you have three people on each side, each of whom is a 200-pound man, so three, 200-pound men on each side, but it just so happens that on one side those men are NFL linebackers, on the other side they are 200-pound couch potatoes.

So, there, even though numerically balanced, you know who is going to win that tug of war every time, because

of the strength of those individuals on one side. Actually, in order to be able to approach that numerically, there is something called the Z statistic, and that is what we will show next.

[Slide.]

Actually, the Z statistic is based on two factors. One is the numerical imbalance between treatment arms, so-called Zd, and the other is the impact of that factor, so-called Zj, so that the potential bias due to the factor is known as a Z product, and so that the potential bias introduced by steps 1 and 2 combine, so that large products translate to more potential bias.

That is shown on the next slide when we actually look at the Z statistics for those prognostic factors.

[Slide.]

Here, you can see even though the numerical imbalance was not very large, the impact of alkaline phosphatase was very large for the largest Z product. In addition, imbalance here was small, impact was large and significant, and WHO performance status, as you might recall, was PS2 of 11 percent on each arm, so they are numerically equivalent even though there was a significant impact of performance status, as we all recognize, the overall bias on one side or the other was not there.

So, that actually tries to address your concern

about how did we get from a very small numerical imbalance to a significant prognostic factor.

DR. KELSEN: I think what it says is that the bulk comes from alk phos.

DR. ROTHENBERG: Yes.

DR. SCHILSKY: Dr. Margolin.

DR. MARGOLIN: This is probably to Mace, but it is regarding a completely separate question, which is to clarify what the rationale was, presumably based on some desire to take advantage of this synergy in laboratory analyses, the rationale for the addition of oxaliplatin in the two first salvage studies that were shown, the de Gramont regimen, and I think one of the other regimens, in patients who were 5-FU and folinic acid failures.

Traditionally, we see so little when we do that, and it can enhance the toxicity and maybe obscure our ability to see the true effect or true benefit of a salvage drug. So, I wonder what the rationale was.

DR. ROTHENBERG: The question was what the rationale was for continuing on a drug on which patients had previously progressed. I think it was a combination of factors. Is that the correct question?

I think it was due to a combination of factors. One is some of the preclinical data that I showed and some that I did not show from Fischel and colleagues, but also

from clinical practice, and that is also shown in some of the monotherapy studies that I showed you.

In the front-line monotherapy studies, the response rates were in the 10 to 15 percent range, or actually the 13.2 percent range, and then when we combined that with 5-FU, response rates in the trials--and actually we can pull up EFC 2917 and 2964 to show you those response rates, as well, were significantly higher.

It was the overall impression of the investigators who were working with the drugs from those experiences that the drug seemed to work better when used.

[Slide.]

Here is 2964 and 2917 with response rates from 7 to 23 percent.

[Slide.]

If we now show the monotherapy studies, the summary slide for them, here, response rates are somewhat similar, but this is for previously treated actually is what we should be looking at, is only 7 to 10 percent here.

So, the overall impression was that this was a drug that appeared to be more effective when given in combination with 5-FU, and it was a follow-up to the preclinical data suggesting that this indeed was the same.

The mechanism of interaction right now is undergoing study and certain of the hypotheses, for

instance, that one drug change the other drug's pharmacology, has not been borne out, that oxaliplatin might inhibit DPD has not been borne out. Actually, Dr. Paul Juniwitz can actually address some of the additional preclinical data on the nature of this interaction.

MR. MOYER: Is that something you would like to see in the preclinical data in addressing your question?

DR. SCHILSKY: Not at this time.

Dr. Simon.

DR. SIMON: At this point I am going to limit myself just to questions. I feel like I have more to say about comments later. I feel like your presentation has sort of violated so many of the basic principles of good statistical practice that I am sort of shocked, but I do want to ask a couple of just specific questions.

One, could you explain more about what you have done with the minimization, was there any random element in the treatment assignment procedure, or was this minimization as originally published by Tabes in which it was totally deterministic?

MR. MOYER: Your question is regarding the minimization technique utilized in 2962. Dr. Bigelow from our statistics group will address that question for you.

DR. BIGELOW: In response to the question, the minimization was deterministic.

DR. SIMON: So, this was really not a randomized study at all, because not only did you--you stratified by center--how many centers were involved?

MR. MOYER: Thirty-six or 37--37.

DR. SIMON: So, you had a large number of centers, relatively small number of patients in many of the centers, deterministic treatment assignment, probably totally decipherable to the physicians entering patients.

The other specific question I want to ask is about censoring. This strikes me as essentially immature data which should not even be presented to the FDA at this point for the pivotal study.

You had 90 patient censored in this survival analysis on the oxaliplatin arm, and 79 patients censored in the survival analysis of the control arm with a median follow-up of only 20 months, and the data was up to date as of July of 1998.

I guess I have two questions. Why aren't we seeing more up-to-date data? Is it because you had some stipulation that you didn't want to pay to follow patients for more than 35 months?

MR. MOYER: No. Actually the per-protocol analysis was 35 months follow-up of patients, so the July 8th, 1998 was the per-protocol analysis.

DR. SIMON: Why was the 35-month stipulation made?

What that means if you make that stipulation, it means that for many of the more recent patients, you have the report follow-up.

MR. MOYER: Because progression-free survival is the primary endpoint, we applied the same rules for that to the final survival analysis.

Dr. Bigelow, would you like to address that any further?

DR. BIGELOW: The protocol clearly stated that the follow-up of all patients was to be stopped 35 months after the first patient was enrolled, and we felt that that was a predetermined cut-off date for the survival analysis, and that is the date that we--

DR. SIMON: That almost guarantees that we are asked to sort of review data for an immature study with inadequate follow-up. It is adequate maybe for the first patient who went on the study, but it is not adequate for the mass of patients who went on the study later in the trial.

The other question I want to ask is of the 90 censored patients on the oxaliplatin arm and the 79 censored for survival on the control arm, were any of these patients censored for any reason other than that you reached your July 8th, 1998 cut-off date? Were any of them censored because you couldn't contact them, they took other

treatments, any other reason?

DR. BIGELOW: With regard to the censoring, all but a few patients were brought to the cut-off date. I believe there were a few that were lost to follow-up earlier than that, a couple a week early, and I think maybe one, two or three weeks early. We made a lot of effort to get up to that cut-off date.

DR. SIMON: So, there were no patients censored for, you say, for taking other treatments or progressive disease going off study, you are not tracking them?

DR. BIGELOW: If the patients went off study, they were still followed in the intent-to-treat analysis until we did the primary analysis, intent-to-treat, assuming that everything that happened off study, you know, was relatable to the randomized treatment.

DR. SIMON: What does that mean?

DR. BIGELOW: You are asking what intent to treat means?

DR. SIMON: No, what does it mean your final statement, as long as it was relatable, did you say assuming? What does he mean, assuming it was relatable? You are just saying you did not censor anyone for going off study regardless of what treatments they received or anything up to that point?

DR. BIGELOW: That's right.

MR. MOYER: We have continued to follow that study, and we do have an updated analysis.

DR. SIMON: You do have an updated survival analysis?

MR. MOYER: Yes, from the December '98 cut-off, another almost six months, if you would like to see that. Would you like to see that?

DR. SIMON: Yes.

MR. MOYER: Dr. Rothenberg, do you want to go through that for us?

DR. ROTHENBERG: This is the same data from the pivotal trial 2962 with a data cut-off date of December 1, 1998.

[Slide.]

The median survival of the--actually, the relationship has not changed very much. As you can see, the mean survival of the control arm, 14.7 months, for the oxaliplatin arm, 16.2 months. Hazard ratio remains exactly as it was before for the unadjusted survival, for 0.83.

DR. SIMON: Thank you.

MR. MOYER: That data just became available to us and has not been submitted as part of the NDA at this point in time, so we would have to do that.

DR. SCHILSKY: Other questions? Dr. Albain.

DR. ALBAIN: Do you have any pilot data yet

available on combination of this agent with the so-called Mayo regimen? Are those studies in progress, where do they stand at this point?

MR. MOYER: Those studies are in progress, and I could actually ask Dr. Richard Goldberg from the Mayo Clinic in the 6C study that is going on through the intergroup effort.

DR. GOLDBERG: I will need the three slides that address the toxicity data.

[Slide.]

We have really only preliminary data from the 6C trial. The 6C trial is an intergroup trial that is currently open to all of the members of the intergroup. It has as its goal 1,800 patient accrual.

To date there are 377 patients entered as of Monday, and we have data on them, approximately 183 with regard to preliminary toxicity, and this is that data.

Now, just to outline the protocol for those of you who aren't aware of it, there are six arms in.this study. One arm is the Mayo control, the 5-FU/leucovorin given as bolus. Then, there are two arms looking at scheduling of CPT-11/5-FU/leucovorin, two arms looking at scheduling of oxaliplatin 5-FU/leucovorin, and one arm looking at oxaliplatin and CPT-11 with no 5-FU.

The preliminary data here shows that on the bolus

regimen of the oxaliplatin/5-FU/leucovorin, the toxicity for nausea and vomiting has been 5 percent, which is not out of line for what is seen with the other arms of the study.

Diarrhea has been 24 percent, similar again to the toxicity seen with four of the arms. Stomatitis has not been a problem. Dehydration has been a problem that has been similar to the others. I would also note on this that the regimen for which the company is seeking approval has had a very low toxicity to date. This regimen is not the one that they are seeking approval for today.

[Slide.]

In addition, with respect to neutropenia, neutropenia is common although as has been indicated in the prior discussion, it is not always clinically significant, you could even say not often clinically significant, and the rate of neutropenia is I think comparable among the regimens.

Febrile neutropenia is more common with the bolus Mayo regimen without oxaliplatin or with the CPT-11/5-FU/ leucovorin-containing regimen, and thrombocytopenia has not really been much of a problem.

[Slide.]

Finally, as you would expect, neurotoxicity is infrequent with non-oxaliplatin-containing regimens, and frequent--and this is all grades of neurotoxicity in the top

column, and Grade 3 neurotoxicity is noted here. So, as has been the experience by Dr. de Gramont in his studies, dose-limiting toxicity in the regimen under discussion today has been neurotoxicity. It is less frequent when it is combined with the Mayo regimen.

Does that address your question?

DR. ALBAIN: Yes. Thank you.

DR. SCHILSKY: Thank you. Dr. Sledge.

DR. SLEDGE: In your adjusted analysis, including the organs involved, PS and baseline alkaline phosphatase, for those of us who are too unsophisticated to be able to explain what a hazard ratio means to a patient, could you tell me what the median improvement in survival is in your adjusted model?

MR. MOYER: The improvement in survival?

DR. SLEDGE: Yes.

MR. MOYER: Dr. Bigelow, do you want to address that? It translates to a 30 percent reduction in the potential for the risk of death.

DR. SLEDGE: What does that mean?

MR. MOYER: Dr. Bigelow, do you want to explain what that means mathematically?

DR. SLEDGE: No, clinically. What is the improvement in survival? What is the difference in median survivals?

MR. MOYER: Your question is what it means clinically.

DR. SLEDGE: You don't have to explain hazard ratios to me, just explain what the difference in median survival is.

DR. BIGELOW: In the adjusted curve?

DR. SLEDGE: In the adjusted curve.

DR. BIGELOW: I believe the median for the control becomes 14 months, and for the treatment arm it is 15.5 months. They are slightly larger than they are in the unadjusted.

DR. SLEDGE: So, about a month and a half.

DR. BIGELOW: Yes, I think so.

DR. SCHILSKY: Dr. Lippman.

DR. LIPPMAN: In the 2961, the overall survival analysis unadjusted was not significantly worse for oxaliplatin, and then after adjusting for post-study therapy, it is not significantly better.

Is the main thought--maybe Mace can handle it--for this is the difference in oxaliplatin use, 64 percent?

The other question is what the response rate was in the group of patients that got post-therapy oxaliplatin.

DR. ROTHENBERG: Your first question relates to the--I am sorry?

DR. LIPPMAN: It seems as though the reason the

curves switched from nonsignificantly worse to nonsignificantly better is because of the 64 percent oxaliplatin use?

DR. ROTHENBERG: Right.

DR. LIPPMAN: In the post-therapy, and so if that is what you believe, I guess the question is what was the response rate in that group?

DR. ROTHENBERG: In the patients who received second-line oxaliplatin, okay, we have that information. We will try and pull it up for you.

[Slide.]

This doesn't tell you what the response rate is. The response was 10 out of 58. I don't know what the math was on that, the patients who got second-line oxaliplatin, so pretty consistent with prior experience.

DR. SCHILSKY: Dr. Nerenstone.

DR. NERENSTONE: Just a brief clinical question. In your patient regimen with the 5-FU bolus continuous infusion, how is that given? Were people required to have central lines, was that given through a pump, and was hospitalization required?

DR. ROTHENBERG: The de Gramont regimen does require a reliable catheter, so they do require semi-permanent catheter placement. The patients are all treated in the outpatient setting. The oxaliplatin and the folinic

acid are both given as two-hour infusions on the first day, followed by a bolus of 5-FU, followed by a 22-hour infusion of 5-FU.

The next day the patient returns to clinic, and then gets a two-hour infusion of folinic acid, bolus of 5-FU, and another 22-hour infusion of 5-FU, and then they are disconnected often at home, so it is all outpatient.

DR. NERENSTONE: And in terms of your toxicity, do you have any discussion about catheter problems, leakage problems, infection, or poor clotting?

MR. MOYER: Dr. Haller can address that from the safety perspective, and he has the most patients in that trial, as well, but he will address it from experience.

DR. HALLER: We don't have a slide representing the numbers, but the actual experience for discontinuation for technical reasons was actually quite small. It was under the adverse events, and so in the original pivotal trial, there were two or three patients who stopped because of problems with catheter-related incidents.

In my own practice, I have had none out of 130, so it is about the same as you would expect with any infusional regimen where you required a 48-hour infusion every two weeks, I think no greater, no less.

DR. SCHILSKY: We are going to take just a few more questions. Dr. Kelsen, go ahead first.

DR. KELSEN: Mace, in 2961, there were a number of patients who had salvage surgery. I think you were about to show us that slide when it flashed off the screen.

How many of those patients were able to be converted to completely resectable? I know this is hard, but do you have any feel for how many were completely unresectable at the initiation or were they borderline resectable? These were all from the French center, from Dr. Bismuth's group?

MR. MOYER: Yes. Your question is regarding the number that might have been resectable at baseline and then how many were--

DR. KELSEN: If you can convert somebody who has unresectable disease to resectable disease and a potential for long-term disease-free survival, that is an important observation. I just sort of wondered what the numbers were.

DR. ROTHENBERG: We don't have the numbers for the patients who were grossly unresectable versus borderline. We do have a slide that does talk about the treatment effect, how many patients were able to be resected after front-line and salvage therapy, so I will walk you through this.

[Slide.]

In the control arm, 58 out of the 100 patients got second-line oxaliplatin-containing chemotherapy. Second

line, other treatments, CTP-11, other 5-FU were a bit more common in the oxaliplatin arm. About 30 percent of patients in the control arm versus 57 patients on the oxaliplatin arm got no further systemic treatment.

The number of patients who can undergo complete surgical resection after first-line chemotherapy versus those who underwent surgery, but had incomplete resection are shown here.

The important thing here is that only 21 patients out of the 100 who got 5-FU/folinic acid were felt to be potentially resectable for cure at the time of the end of that front-line therapy versus 32 patients on the oxaliplatin arm.

When we look at the number of patients who were completely resected following front-line therapy, it was 21 patients out of 100 for the oxaliplatin arm, 17 patients out of 100 for the control arm.

Interestingly, then, when you follow them along and look at second-line chemotherapy attempts, 14 patients who could not be approached for surgical resection after front-line therapy could be approached after second-line therapy, 6 of them had complete surgical resection.

So, in that way, overall, the number of patients who could undergo complete surgical resection was 23 in the control arm. That takes into account the second-line

treatment effects. And 21 in the oxaliplatin-containing arm.

DR. KELSEN: And that second-line treatment is oxaliplatin?

DR. ROTHENBERG: Well, it was oxaliplatin in some, but it was also CPT-11 and other 5-FU treatments.

DR. SCHILSKY: Dr. Johnson.

DR. D. JOHNSON: This question can go to any of the presenters, but I think what I have heard so far today is a pretty strong presentation from the standpoint of convincing me that oxaliplatin has some sort of activity in colorectal carcinoma.

The sponsor, however, is seeking an indication for first-line therapy, and as a clinician, I am struggling with how I am going to present this to my patient for whom 5-FU and leucovorin could be the alternative irrespective of how I choose to give it. We can put that aside for the moment.

I am struggling with what it is that is going to convince me to give this as front-line therapy, since you have not shown us a survival advantage, and I would yield to Dr. Simon's expertise in this area, and I would like to look at not the adjusted, but the unadjusted survival curves.

If I give oxaliplatin upfront, what I have seen is a lot more toxicity, and I haven't seen a survival benefit, so if I could maybe hear from the group as to why I would